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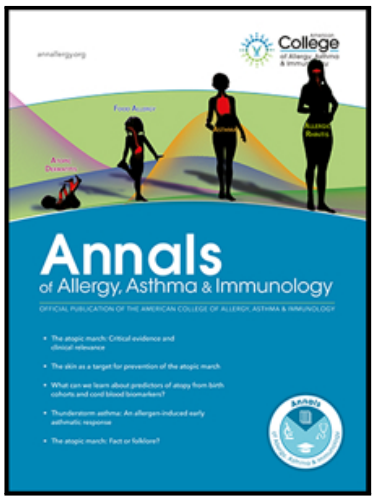

Allergic reactions to COVID-19 vaccines and addressing vaccine hesitancy: Northwell Health experience

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Conflict of Interest:

Blanka Kaplan, Sherry Farzan, Gina Coscia, David W. Rosenthal, Alissa McInerney, Artemio M. Jongco, Punita Ponda - No disclosures

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COVID-19 vaccines; Moderna; Pfizer-BioNTech; allergic reactions; adverse reactions; polyethylene glycol (PEG) challenge; PEG skin testing; vaccine hesitancy

Abbreviations used:

COVID-19 - coronavirus disease 2019CDC - Centers for Disease Control and Prevention

PEG - polyethylene glycol

ED - Emergency Departments

PODs - Point of Dispensing

CARES- Northwell COVID Ambulatory Resource Support program

NIAID - National Institute of Allergy and Infectious Disease

Background: Allergic and nonallergic adverse reactions have been reported with global coronavirus disease 2019 (COVID-19) vaccination. It was previously hypothesized that polyethylene glycol (PEG) may be responsible for anaphylactic reactions to mRNA COVID-19 vaccines.

Objective: To report the workflow established at our institution, types, and frequency of adverse reactions to mRNA COVID-19 vaccines in patients presenting for allergy evaluation.

Methods: A COVID-19 vaccines adverse reactions registry was established. We used PEG prick skin testing, followed by PEG challenges in selected cases, to ensure PEG tolerance and encourage completion of COVID-19 vaccination series.

Results: A total of 113 patients were included. Most vaccine reactions (86.7%) occurred in women. Anaphylaxis occurred only in women, all of which had a history of allergic disease and two-thirds had asthma. Anaphylaxis rate was 40.6 cases per million. None of the anaphylactic cases developed hypotension, required intubation or hospital admission. Systemic allergic symptoms, not fulfilling anaphylaxis criteria were significantly more common in Pfizer-BioNTech than Moderna vaccinated patients (p=0.02). We observed a higher incidence of dermatologic non-urticarial reactions in men (p=0.004). Among first dose reactors, 86.7% received and tolerated second dose. We observed a high rate of false positive intradermal skin tests and frequent subjective symptoms with oral PEG challenge.

Conclusion: Intradermal PEG testing has limited utility in evaluating anaphylaxis to mRNA vaccines. Most severe postvaccination allergic symptoms are not caused by hypersensitivity to PEG. The majority of people with reaction to the initial mRNA vaccine can be safely revaccinated. Patients with anaphylaxis to COVID-19 vaccines benefit from physician-observed vaccination.

Introduction

As of October 1, 2021, over 233 million coronavirus disease 2019 (COVID-19) cases and over 4.77 million COVID-19 related deaths have been reported. Highly immunogenic COVID-19 vaccines offer robust protection,[1,2] and are powerful tools to control the pandemic. Within the first few days of international vaccination efforts, systemic allergic reactions were reported at rates higher than those with other vaccines.[3-5] Consequently, in December 2020, the Centers for Disease Control and Prevention (CDC) recommended against vaccinating people with severe or immediate allergic reactions after a dose of a COVID-19 mRNA vaccine, or any of its components, and suggested referral to an allergist-immunologist for further evaluation.[6, 7] It has been hypothesized that polyethylene glycol (PEG) may be responsible for anaphylactic reactions to the COVID-19 mRNA vaccines,[8] and initial guidance on risk stratification and management of patients allergic to the mRNA vaccines, was based on PEG testing.[9]

While multiple factors contribute to vaccine hesitancy, concern about adverse effects is one of the leading causes of vaccine refusal and delay in vaccination.[10] As allergists, we addressed

patients' questions about allergic and other adverse reactions to COVID-19 vaccines to minimize vaccine hesitancy. We evaluated patients with reported reactions, performed testing and challenges where applicable, and provided counseling about risks and benefits of vaccination. Here we report our experience and the types of adverse reactions to COVID-19 vaccines seen for consultation in the Division of Allergy and Immunology at Northwell Health, which employs more than 74,000 people in 23 hospitals and more than 700 outpatient settings.

Methods

Study design

Patients referred to be seen in our office for COVID-19 vaccine reactions from January 2021 through May 2021 were prospectively evaluated. A COVID-19 vaccines adverse reactions registry for people who had adverse reactions and were evaluated in the Division of Allergy and Immunology was established. Demographic data, details of adverse reactions to COVID-19 vaccination and allergy evaluation, previous allergic and relevant medical history, were included in the registry. This study was approved by the Institutional Review Board of the Feinstein Institutes of Medical Research at Northwell Health. Written consent was obtained.

Referrals and Education

With the initiation of the national COVID-19 vaccination program, we established a referral process for vaccine reactions via collaboration with the Northwell Employee Health System, Emergency Departments (ED), vaccination PODs (Point of Dispensing), ambulatory physicians,

hospitalists and the Northwell COVID Ambulatory Resource Support (CARES) program (Figure 1). Education was provided by our faculty to Emergency Department (ED), ambulatory and hospital medicine faculty regarding COVID-19 vaccine reactions, management, indications for allergy referrals, and recognition and treatment of anaphylaxis. An online educational module on identifying and treatment of anaphylaxis was developed as an additional resource. Our staff attempted to contact every patient referred. Individuals with a reported vaccine reaction were triaged over the phone by the allergy fellows-in-training and telehealth or in-person visits were scheduled within a week with one of the six faculty attending physicians. People with acute allergic postvaccination symptoms were seen within 24 hours. A thorough history was obtained and recommendations for further evaluation and/or COVID-19 vaccination, based on current knowledge, CDC guidance[11] and communications from AAAAI/ACAAI,[12,13] were provided. Depending on the type of reaction and history, office visits for skin testing were scheduled. In-office oral challenges to PEG (MiraLAX®) were offered in select cases. Management algorithms for different types of COVID-19 vaccine reactions were developed and adapted as our knowledge evolved. A high-risk vaccination clinic was established for patients who had a reaction to the first dose and patients with concerns about allergic reactions to COVID-19 vaccines, who preferred to receive vaccination under an allergist's supervision.

Types of Reactions

Given the wide variety of adverse reactions observed, we devised a system to classify the types of reactions (Table 1) into six different groups, using the most significant presenting symptom(s). This classification scheme was based on the types of reactions observed and

intended to risk-stratify patients, streamline management of vaccine reactions and facilitate referrals for allergy evaluation, without delaying the second vaccination for people with mild reactions. Groups 1 and 2 included patients with immediate and delayed nonallergic reactions, respectively. Group 3 included patients with various dermatologic symptoms, except generalized urticaria, which was classified in group 5. Patients with subjective tongue and/or throat swelling, and hoarseness were included in group 4. Although the exact mechanism for each patient is difficult to decipher, these symptoms are very disturbing to patients and necessitated an allergy evaluation to exclude hypersensitivity reactions. Group 5 included patients with allergic symptoms, suggestive of IgE-mediated sensitivity. In order to be assigned to Group 6, the patient was required to meet criteria for anaphylaxis according to the Brighton Collaboration case definitions,[14] the National Institute of Allergy and Infectious Disease (NIAID) and Food Allergy and Anaphylaxis Network criteria for anaphylaxis,[15] or both. The designation of anaphylaxis was confirmed by three of the authors (BK, GC, SF).

PEG3350 skin testing and (MiraLAX®) Challenges for mRNA vaccine reactions

Skin prick and intradermal testing was performed in patients when there was a concern for an IgE-mediated process after COVID-19 mRNA vaccination. Patients with no suspicion for immediate hypersensitivity reaction were not offered skin testing and were cleared for the next vaccine dose. Testing protocols were adapted from Banerji et al.[9,16] For patients with negative or inconclusive skin testing to PEG3350, and concern for a risk of reaction to the mRNA vaccine, an in-office oral graded challenge to PEG3350 was offered. Seventeen grams of PEG3350 was diluted in 250mL of water. Two-dose (10%, 90%) or three-dose (1%, 10% and 89%) challenges

were performed, with doses administered 30 minutes apart. Patients were observed for 60-90 minutes afterwards for the development of signs or symptoms of an acute allergic reaction. We also used a single-blind placebo-controlled PEG3350 challenges in some patients to minimize false-positive results. Skin testing to COVID-19 vaccines was not performed because the United States Food and Drug Administration required an expanded access investigational new drug (IND) application for COVID-19 vaccine skin testing, challenge and desensitization due to the emergency use authorization (EUA) status of the vaccines. To comply, we requested letters of authorization from the manufacturers which were not granted. Patch testing to PEG was performed in patients with delayed non-urticarial rashes.

Statistical Analysis

Summary descriptive statistics were calculated for demographics, vaccine type and reaction classification for mRNA vaccines. Incidence of anaphylaxis was calculated based on employee immunization data within the Northwell Health System. The difference between two independent proportions was utilized to compare the proportion of vaccine reactions in each category between the Pfizer-BioNTech and Moderna vaccine groups, using an "N-1" Chi-squared test as recommended by Campbell (2007) and Richardson (2011) with MedCalc.[17]

Results

Types of reactions to COVID-19 vaccines

Since December 2020, 212 individuals were referred for COVID-19 vaccine reactions and 114 were evaluated by the Division of Allergy & Immunology faculty. Among the remaining 98 patients, we were unable to reach eighty-three, ten patients no showed and five cancelled their appointments. Of the 114 evaluated, one patient with anaphylaxis was excluded from our analysis because her symptoms started on day 4 after receiving her first Pfizer-BioNTech vaccine, making direct association with the vaccination unclear. Of the 113 patients, 62 had reactions after receiving the Pfizer-BioNTech, 50 after Moderna and 1 after receiving the Johnson & Johnson's/Janssen (J&J/Janssen) COVID 19 vaccines (eTable 1). Mean age was 48 years (range 19-89 years) and the majority of patients were female, 98/113 (86.7%). Among 112 patients who received mRNA vaccines, 105 presented after the reaction to the first dose and 7 patients reacted to their second dose (four to Pfizer-BioNTech and three to Moderna) after tolerating the first. Some differences were noted between the Moderna and Pfizer-BioNTech vaccines with respect to the types of reactions. (Figure 2). Delayed nonallergic adverse reactions occurred more frequently in Moderna-vaccinated patients (p=0.01). This difference was primarily due to injection site reactions that were observed in 10/13 Moderna-vaccinated patients, but in none of the patients who received Pfizer-BioNtech. Systemic allergic symptoms (generalized pruritus, urticaria, angioedema, wheezing) were higher in Pfizer-BioNtech vaccinated patients (p=0.02). None of the patients had stridor or required hospitalization. We did not identify any significant differences between mRNA vaccines for other types of adverse reactions. In our cohort, 47% (7/15) males developed dermatologic nonurticarial reactions while only 15% (15/97) of females had these symptoms. (p=0.004)

Anaphylaxis

Eight patients, all women, had anaphylaxis based on Brighton or NAIAD criteria, or both (Table 2). Six cases (75%) of anaphylaxis occurred after the first dose of mRNA vaccines and one each (12.5%) after the second vaccination (Moderna) and single dose J&J/Janssen vaccine, respectively. None of the patients who had anaphylaxis developed hypotension, required intubation or hospital admission. The anaphylaxis rate was calculated based on four Northwell Health System employees only, given available data. Combined anaphylaxis rate for both Moderna and Pfizer-BioNTech vaccines was 40.6 cases per million doses administered, with 28.3 and 71.6 cases per million doses administered for Pfizer-BioNTech and Moderna, respectively (Table 3). The anaphylaxis rate didn't differ between two mRNA vaccines.

PEG testing and challenges

We initially implemented the suggested skin testing algorithm.[9] One patient with anaphylaxis to Pfizer-BioNTech vaccine, had positive prick skin test to PEG (Table 2). Eighteen patients had methylprednisolone acetate skin testing performed at recommended concentrations and in six of them (33%), the skin test was positive. Three of these six patients (50%) had a subsequent negative PEG challenge and tolerated their second mRNA vaccine (Figure 3). Seeing a high rate of false-positive tests to methylprednisolone acetate, we decided to proceed with graded PEG challenges after negative PEG prick skin test for patients with an unconvincing history of PEG allergy (Table 4). Ten of 23 (43.5%) patients developed mild, transient symptoms during the PEG3350 challenge. Symptoms included scratchy throat, tingling, numbness of the tongue and palate, sweet taste in the mouth, feeling of swollen tongue, lips, lump in the throat, throat closure sensation, shortness of breath, skin itching and blotching, lightheadedness, and dizziness. All

symptoms were subjective, except skin blotching that occurred only in people with history of chronic and intermittent hives. These symptoms were transient, mostly subjective and were not treated, except in one patient with history of urticaria, who developed pruritus and received fexofenadine 180 mg with resolution of symptoms. In some cases, symptoms experienced by an individual during PEG challenge were similar to those experienced by that patient with vaccination. Patients were reassured, educated, and cleared for their second dose with premedication. PEG patch testing was performed and was negative in three patients with delayed rashes.

Pretreatment prior to vaccination:

As per published guidance,[9] patients with mild allergic symptoms to the first COVID-19 mRNA vaccine were pretreated with non-sedating antihistamines (e.g. cetirizine 10-20 mg or fexofenadine 180-360 mg 1 hour prior to vaccination). Asthma and chronic urticaria medications were optimized to control underlying conditions. Patients were instructed to take additional doses of cetirizine or fexofenadine for post-vaccination pruritus and rashes. Patients with delayed rashes were recommended to continue antihistamines for a few days (1-2 days longer than duration of the rash after the 1st dose). Patients with history of subjective feeling of throat and tongue swelling, were premedicated with anti-reflux medications (H2 blockers or proton pump inhibitors). Patients with asthma, who had respiratory symptoms with the first dose, were instructed to take Albuterol HFA 2 puffs prior to their second dose.

Administration of the second dose:

Among 105 patients who reacted to the first dose of COVID-19 mRNA vaccines, 91 (86.7%) completed their vaccination series without any severe immediate reactions (Figure 3). Among six patients with anaphylaxis to the first dose of mRNA vaccine, five received the second dose of the same mRNA vaccine (Table 2). Four of these patients tolerated vaccination without any allergic symptoms and one patient developed isolated cough (Patient 4). One patient with history of anaphylaxis to the first dose, had a positive PEG prick skin test and a positive intradermal test to Triamcinolone acetonide (contains Polysorbate 80) and did not complete two-dose vaccination series (Patient 1). Notably, the latter two patients had protracted allergic symptoms for days after the first dose.

Discussion

Despite the extremely low rate of anaphylaxis to COVID-19 vaccines, public concern about adverse effects, including allergic reactions remains high, contributing to vaccine hesitancy. Our experience underscores that the majority of people with allergic symptoms after their initial mRNA vaccine can be safely revaccinated with premedication and hypersensitivity to PEG is not the culprit in most cases of severe allergic symptoms.

The rate of anaphylaxis to in our cohort is 40.6 cases per million, while previously reported rates of anaphylaxis to COVID-19 mRNA vaccines vary from 4.5 per million, reported by CDC[18] to 247 cases per million doses administered after the first vaccination, reported at Mass General Brigham.[19] The estimated rate of anaphylaxis to non-COVID-19 vaccines is significantly lower, 1.31 per million vaccine doses[5]. The differences in reported anaphylaxis rates can be explained by the extremely low incidence of anaphylaxis to vaccines, variability in applying anaphylaxis

criteria and different populations studied. We believe that misdiagnosis and mistakenly assumed causality leads to overestimation of anaphylaxis rate. For example, a patient who developed shortness of breath two hours after vaccination and required intubation, was referred for evaluation of presumed COVID-19 vaccine anaphylaxis. This patient did not have any associated allergic symptoms and was diagnosed with bilateral pneumonia, asthma and acute on chronic respiratory failure. Respiratory failure alone does not fulfill anaphylaxis criteria, tryptase was not checked and the relationship to vaccination is unclear. Also, causality is uncertain for a patient, who developed anaphylaxis four days after vaccination and was thus excluded from our analysis. The reported rate of anaphylaxis to COVID-19 vaccines has been decreasing as the vaccination rate increases and concerns regarding new vaccines diminish, suggesting that anxiety and panic attacks can present with symptoms mimicking allergic reactions, such as shortness of breath, globus sensation, tachycardia and hypertension, and therefore may contribute to a higher reported rate of allergic reactions to COVID-19 vaccines.

In our cohort, anaphylaxis occurred only in women, which is similar to previously reported data.[19,20] There was no statistically significant difference in the rate of anaphylaxis between the Pfizer-BioNTech and Moderna vaccines, but the rate of systemic allergic symptoms (generalized pruritus, urticaria, angioedema, wheezing), was significantly higher in the former and the rate of delayed nonallergic reactions was significantly higher in the latter. Delayed injection site reactions in Moderna-vaccinated patients accounted for higher rate of delayed nonallergic symptoms after Moderna. This is easily managed with reassurance, anticipatory guidance with clear recommendations about symptomatic treatment (Table 1). The reason for higher rate of systemic allergic symptoms in Pfizer-BioNTech-vaccinated patients in our cohort may be due to different excipients in the mRNA vaccines, but these findings should be confirmed by larger

studies. Every patient with anaphylaxis to a COVID-19 vaccine had a history of atopy and two-thirds had asthma. Underlying asthma and urticaria may contribute to post-vaccination respiratory and cutaneous symptoms, which highlights the importance of optimizing asthma control and that of other underlying diseases prior to immunization. We want to emphasize that in our cohort no one required intensive care or hospital admission. Interestingly, while most allergic and nonallergic vaccine reactions occurred in women, our data indicate that delayed nonurticarial cutaneous reactions may be higher in men. Further research is needed to uncover the etiology for this observed difference in presentation between genders, but experience from other vaccinations has documented higher rates of adverse reactions, including anaphylaxis, in women.[21,22]

Skin testing to the culprit vaccine and its components is the gold standard in evaluating patients with vaccine allergy.[23] Since the predictive value of COVID-19 vaccine skin testing is unknown, and PEG, which is reported to cause rare cases of IgE-mediated reactions, including anaphylaxis, is the only component of mRNA COVID-vaccines that can be tested at this time, initial risk stratification pathways were based on excipient skin testing to PEG. Skin testing to PEG is not standardized and intradermal PEG skin testing can cause anaphylaxis,[24] therefore PEG-containing methylprednisolone acetate is recommended for intradermal testing. Although PEG and PEG-containing steroid skin testing has been helpful for evaluating immediate hypersensitivity to PEG-containing medications,[25,26] its value in predicting tolerance to COVID-19 mRNA vaccines is unknown. False-positive skin test results may interfere with the ability to clear patients for their subsequent vaccine dose and lead to labeling patients with new drug allergies. Therefore, we utilized oral PEG challenges to clear and encourage patients to receive

their second vaccine doses. Although only 0.06% of oral PEG is absorbed, this results in 10.2 mg of a 17-gram dose, which is much greater than the amount in mRNA vaccines.[27,28] We observed that at least half of the patients with positive methylprednisolone acetate tests went on to tolerate oral PEG and their second dose of an mRNA vaccine, indicating low specificity of this intradermal skin test. Furthermore, negative PEG challenges after presumed hypersensitivity reactions to mRNA vaccines, indicate that PEG is an unlikely cause of severe allergic symptoms in people who don't have a history of anaphylaxis to PEG. However, one of our patients who developed anaphylaxis to the first dose of mRNA vaccine and had protracted symptoms, had positive PEG prick skin test, suggesting that PEG can be a rare culprit and PEG prick skin test may be helpful for evaluating anaphylaxis to mRNA vaccines in selected cases.

Some patients had mild symptoms during their PEG challenge, which sometimes mimicked their symptoms to the initial vaccine. These patients were carefully observed and reassured, and maintenance medications for patients with suboptimally controlled asthma and urticaria were adjusted. Patients were then cleared for their second vaccine dose with premedication. Patients with subjective feeling of "throat symptoms," were additionally empirically premedicated with anti-reflux medications (H2 blockers and/or proton pump inhibitors). All patients (n=91) who went on to receive their second dose, including those with mild symptoms during PEG challenge, tolerated subsequent vaccination with premedication, suggesting that these symptoms are either not allergic, hypersensitivity to PEG is very mild or that there is another allergen within the vaccine that could be triggering reactions.

We established a high-risk vaccination clinic to provide a safe and comfortable setting where patients would receive their second dose under the supervision of an allergist trained to identify and treat allergic reactions. All patients tolerated vaccination, administered as a single dose, with

appropriate premedication. The majority of our patients with anaphylaxis to the first COVID-19 vaccine received second dose at the high-risk clinic. None of these patients had a severe reaction to the second vaccination. Tolerance of the second dose after reported anaphylaxis to the first one has been reported by others[20,29] and suggests a non-IgE-mediated mechanism for most of postvaccination reactions. Other immune mechanisms, including direct mast cell activation by vaccine components and various host factors have been proposed.[30]

Based on our experience, we believe that intradermal PEG testing has limited utility. Prick PEG testing may be helpful in people with history of anaphylaxis to mRNA vaccines. The majority of severe allergic symptoms, associated with mRNA vaccines, are not caused by hypersensitivity to PEG. Special attention should be given to patients with anaphylaxis, followed by protracted symptoms. Although successful administration of the second dose of mRNA vaccine via graded dosing protocol after immediate hypersensitivity reaction to the first dose, has been described,[31] our data suggest that with premedication, the full dose of mRNA vaccines can be administered safely and is well tolerated in most patients. Obviously, this approach will not be appropriate for rare patients with history of anaphylaxis to PEG. Emerging data on mRNA COVID-19 vaccine skin testing suggest that it is safe,[32,33] but may cause delayed reactions at the skin test sites that were not predictive of immediate hypersensitivity reactions to the vaccines.[34] Sensitivity and specificity of vaccine skin testing are still unknown.

With expanding eligibility criteria for vaccination, we have been consulted in increasing numbers for patients with a history of anaphylaxis to medications and vaccines, multiple drug allergies, mast cell disorders, and other allergic concerns, prior to vaccination. We believe that establishing the referral process, educating the healthcare professionals who see the reactions first-hand, and having an allergist evaluate patients early and thoroughly is essential. Initial

allergy evaluation can be successfully done via telehealth visit. Close observation and reassurance for patients who developed mild symptoms during PEG challenges, encouraged our patients to complete their COVID-19 vaccination. The ability to vaccinate patients under the close observation of a physician, trained in recognizing and managing allergic reactions, decreases vaccine hesitancy. As the science about the etiology of the immediate hypersensitivity to COVID-19 vaccines evolves, vaccine skin testing and physician-observed vaccination, will likely become the standard of care for managing patients with COVID-19 vaccine reactions. As allergists, we are well positioned to educate patients about allergic issues and address them before and after vaccination.

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Figure legends:

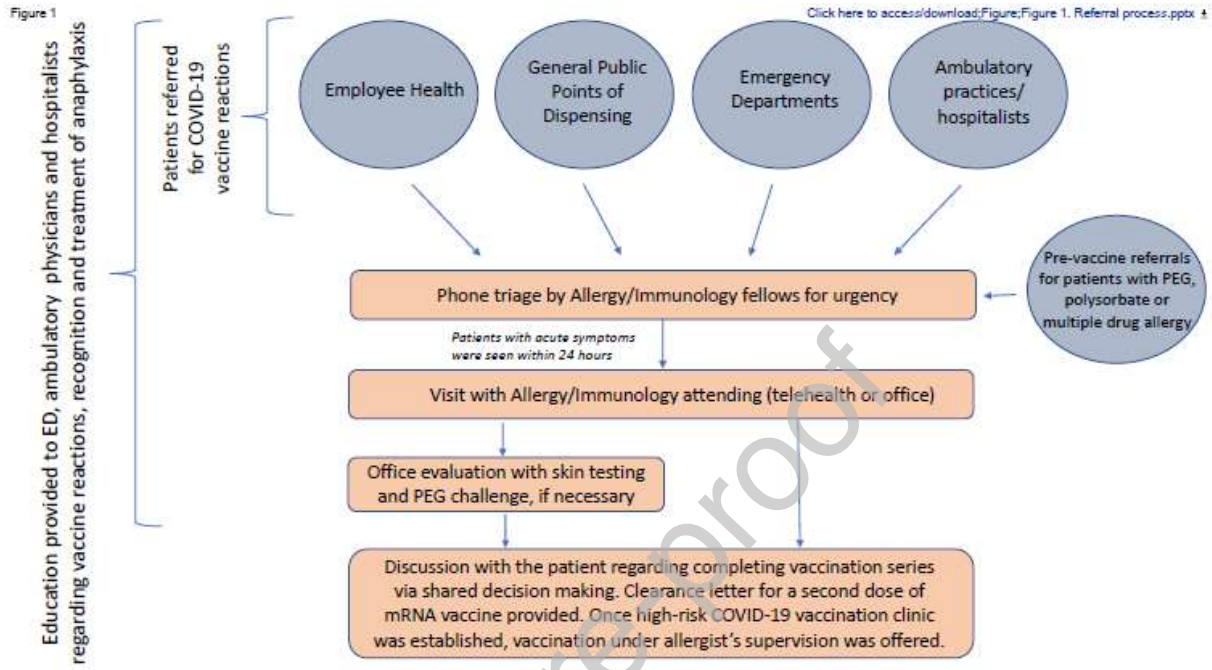

Figure 1 Referral process.

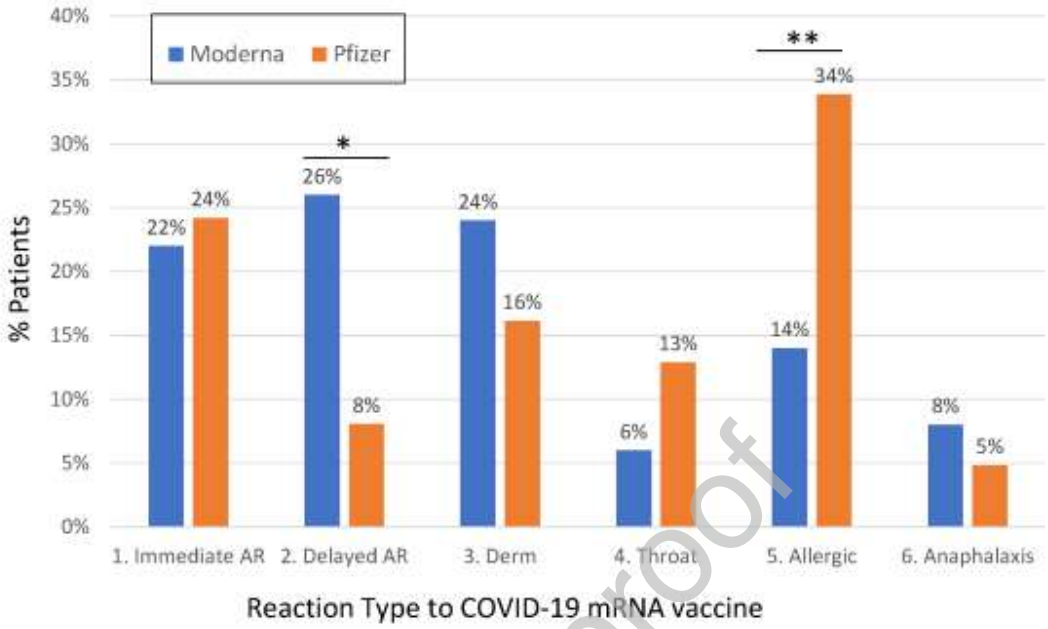

Figure 2 Differences in types of allergic and nonallergic reactions between the Moderna and Pfizer-BioNTech vaccines. Reaction types are defined in Table 1. AR, adverse reactions; Derm, dermatologic reactions.

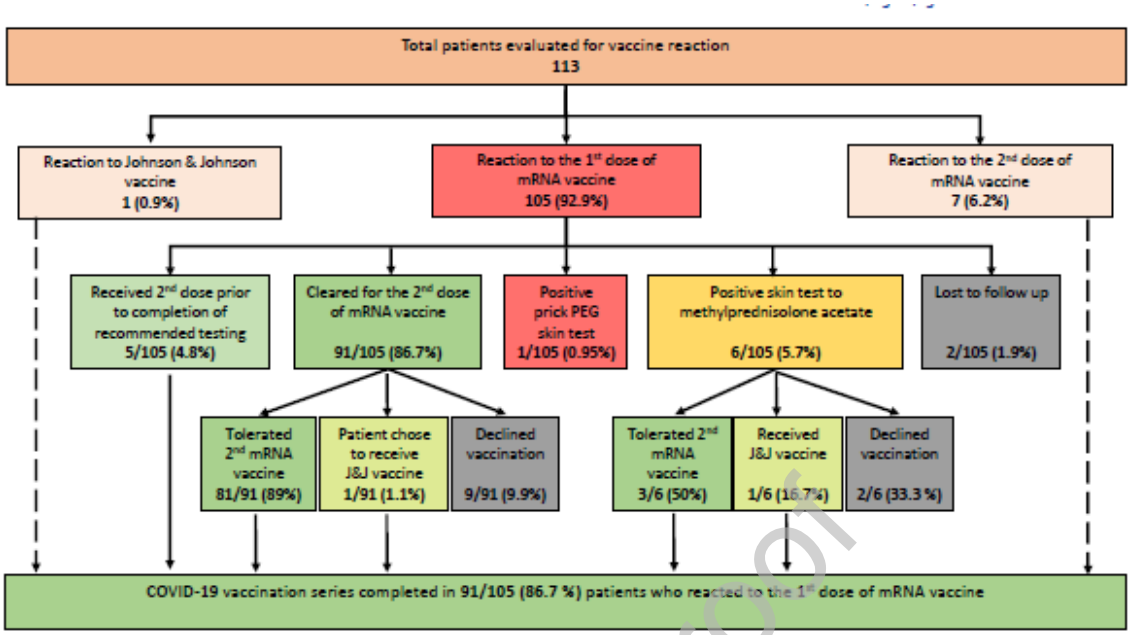

Figure 3 Results of allergy evaluation after COVID-19 vaccination.

Table 1. Classification and action plan for reactions to the first dose of a mRNA COVID-19 vaccine

Group #	Reaction to mRNA COVID-19 vaccine	Proceed with the 2nd dose without allergy consultation	Recommendations for 2nd COVID-19 vaccine, aside of education and reassurance and shared decision making
1	Immediate adverse reactions *(e.g., transient dyspnea, metallic taste, flushing, lip tingling, paresthesia, tachycardia, hypertension)*	Yes	• Consider 30-minute observation for the 2nd dose

2	Delayed adverse reactions *(e.g. injection site reactions, axillar lymphadenopathy on the vaccinated site, expected adverse effects and neurological symptoms*)	Yes	• Symptomatic treatment which can include cool compresses, OTC pain medications or topical treatments, if symptoms recur after 2nd vaccination
3	Dermatologic reactions, excluding generalized urticaria *(e.g. mild transient pruritus and localized rashes: immediate and delayed, and delayed eczematous and maculopapular rashes)*	Yes	• Take antihistamines, such as Cetirizine (Zyrtec) 10 mg or Fexofenadine (Allegra) 1 hour before vaccination. If necessary, can take once or twice a day for a few days as needed (duration of rash after the 1st dose + 1-2 days)
4	Throat symptoms *(e.g. tongue, and throat swelling/fullness, hoarseness)*	No	• Refer for allergy evaluation
5	Systemic allergic symptoms, not fulfilling anaphylaxis criteria *(e.g. generalized intractable pruritus, generalized urticaria, angioedema, wheezing, stridor, need for hospitalization): immediate or delayed*		
6	Anaphylaxis		

Table 2. Characteristics of patients who experienced anaphylaxis

	Age (years)	Past pertinent allergic history	Symptoms of anaphylaxis	Confirmed anaphylaxis		COVID-19 Vaccine	PEG prick skin test	PEG challenge result	Tryptase: reaction/ basal (ug/L)	Notes
				Brighton Criteria	NIAAD Criteria					
1	27	Latex allergy, lip fillers, silicone breas	Generalized hives, SOB, throat and chest tightness, eyelid swelling	Level 2	Yes	Pfizer	Positive at 1:1000 and 1:100	ND	ND/ 4.2	- Protracted symptoms (over a week) - Positive skin test to Triamcinolone acetate (Polysorbate 80) and Hepatitis A (Polysorbate 20)

		t implants								
2	38	Asthma, AR, FA	SOB, chest tightness, cough, tracheal pruritus, dizziness	No	Yes	Pfizer	Negative	Passed	ND/ND	- On dupilumab for asthma - Received and tolerated 2nd dose in high-risk clinic
3	50	Asthma, FA	Generalized pruritus, SOB, tongue and throat swelling, difficulty swallowing,	No	Yes	Pfizer	Negative	Passed	ND/7	- Developed COVID-19 while awaiting 2nd dose - Received and tolerated 2nd dose in high-risk clinic
4	40	Asthma, latex allergy, drug allergy	Generalized hives, SOB, chest tightness, tachycardia	Level 2	Yes	Moderna	Negative	Passed	ND/4	- Protracted symptoms (5 days) - Received 2nd dose in high-risk clinic; 20 min. later developed cough (no other symptoms); post-2nd dose tryptase-3.8
5	46	Asthma, AR, OAS	Generalized hives, chest tightness, abdominal pain, diarrhea, rhinorrhea, facial and eyelid swelling	Level 2	Yes	Moderna	Negative	Passed	ND/ND	- Received and tolerated 2nd dose in high-risk clinic
6	32	Asthma, AR, chronic urticaria, FA	Generalized itching, hives, SOB	No	Yes	Moderna	ND	ND	ND/ND	- Patient declined skin test - Received and tolerated 2nd dose in high-risk clinic
7	34	IVC	Generalized pruritus, urticaria, nausea, felt very lightheaded and weak	Level 2	Yes	Moderna	ND	ND	6/ND	- Tolerated 1st dose; reaction after the 2nd dose
8	48	IVC, FA	Generalized pruritus, lip swelling, SOB, chest and throat tightness, hoarseness	No	Yes	J&J	ND	ND	ND/ND	- 1-dose J&J vaccination completed

AR, allergic rhinitis; FA, food allergy; J&J, Johnson & Johnson COVID 19 vaccine; IVC, Intravenous contrast; ND, not done; OAS, oral allergy syndrome; PEG, polyethylene glycol 3350

Table 3. Rate of anaphylaxis

	After 1st dose		**After 2nd dose**		**Combined, after both doses**	
	Moderna	Pfizer	Moderna	Pfizer	Moderna	Pfizer
Number of anaphylaxis cases, n	1	2	1	0	2	2
Total doses administered, n	14185	36050	13766	34521	27929	70571

Anaphylaxis rate, cases/million doses administered	70.5	55.5	72.6	0	71.6	28.3

This analysis assumes that each reaction is an independent event.

Table 4. Completing vaccination after PEG3350 challenge

PEG-challenged patients	**All patients challenged**	**Developed symptoms during PEG challenge**	**No symptoms during PEG challenge**
Total number of PEG-challenged patients	23	10/23 (43.5%)	13/23 (56.5%)
Tolerated 2nd mRNA vaccine	20/23 (87.0%)	8/10 (80.0%)	12/13 (92.3%)
Patient chose to receive J&J	1 /23(4.3%)	0	1/13 (7.7%)
Lost to follow up	2/23 (8.7%)	2/10 (20.0%)	0

J&J, Johnson & Johnson COVID 19 vaccine; PEG, polyethylene glycol

eTable 1. Demographic and vaccination data

		Moderna	**Pfizer**	**J&J/Janssen**	**Total**
Sex	Female	44	53	1	98
	Male	6	9		15
Age	15-24		3		3
	25-34	4	13		17
	35-44	12	11		23
	45-54	16	24	1	41
	55-64	9	8		17

	65-74	6	2		8
	75-84	2	1		3
	85-94	1			1
Ethnicity / Race	Hispanic or Latino				
	White	4	9		13
	Non-Hispanic or Latino				
	White	29	30		59
	Asian	5	6		11
	Black*	2	7		9
	Other Race	5	6	1	12
	Unknown				
	Unknown	6	3		9

*Black or African American

eTable 2. Number of patients for each type of allergic and nonallergic reactions to mRNA vaccines

Reaction Type	Moderna	Pfizer	Total
1. Immediate AR	11	15	26
2. Delayed AR	13	5	18
3. Derm	12	10	22
4. Throat	3	8	11
5. Allergic	7	21	28
6. Anaphylaxis	4	3	7
Grand Total	**50**	**62**	**112**

AR, adverse reactions; Derm, dermatologic reactions.